TAB A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Savit, et al.		
Serial No.:	10/527,781	Group No.:	3735
Filed:	03/31/2006	Examiner:	Toth
Entitled:	**Noninvasive Nonlinear Systems and Methods for Predicting Seizure**		

DECLARATION OF Robert Savit, Ph.D. UNDER 37 C.F.R. § 1.131

EFS Web Filed
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Examiner Toth:

I, Robert Savit, hereby declare and state, under penalty of perjury, that:

1. I am an inventor of the above-named patent application (hereinafter "present application").

2. In the Office Action dated August 2, 2010, the Examiner cited U.S. Patent Application Serial No. 2004/0122335 (hereinafter, "the Sackerelles patent application") which I understand has a filing date of August 23, 2003 and a priority claim based on a provisional patent application filed August 27, 2002 (U.S. Provisional Patent Application Serial No. 60/406,063 – hereinafter, "the Sackerelles provisional patent application").

3. I reduced to practice in the United States of America the presently claimed invention prior to the filing date of the Sackerelles patent application, and prior to the filing date of the Sackerelles provisional patent application, as evidenced by:

A) the work shown in the attached empirical publication at TAB B (Li, Dingzhou, Zhou, Weiping, Drury, Ivo, and Savit, Robert (2003) Mathematical Biosciences 186 pages 63-77) (hereinafter, "the Li publication"). The work presented in the Li publication was performed in this country by me or under my supervision, prior to August 27, 2002. As evidenced on page 63 of the Li publication, the work presented in the Li publication was submitted to the Mathematical Biosciences

journal on July 25, 2002. As evidenced by the work shown at in the Li publication, the mathematical considerations and experimental results used in obtaining the claimed invention are described. The work shown in the Li publication is represented in the present application at, for example, paragraphs 0092 through 0098, and Examples I, II, and III (paragraphs 0112 through 00149), and Figures 1-9; and/or

B) the work shown in the attached Invention Description at TAB C. The work presented at TAB C was performed in this country by me or under my supervision, prior to August 27, 2002, and was submitted to the University of Michigan Technology Transfer on June 20, 2002.

4. Upon submitting the Invention Disclosure shown at TAB C to the University of Michigan Technology Transfer on June 20, 2002, I worked diligently with the University of Michigan Technology Transfer and the patent attorneys representing the University of Michigan Technology Transfer in preparing and filing the patent application for which the present patent application claims priority (U.S. Provisional Patent Application Serial No. 60/410,695 filed September 13, 2002).

5. I further declare that all statements made herein are of my own knowledge, are true, and that all statements are made on information and belief that are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application of any patent issued thereon.

Dated: 1/13/2011

Robert Savit, Ph.D.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Serial No.:	10/527,781	Group No.:	3735
Filed:	03/31/2006	Examiner:	Toth
Entitled:	**Noninvasive Nonlinear Systems and Methods for Predicting Seizure**		

DECLARATION OF Ivo Drury, M.D. UNDER 37 C.F.R. § 1.131

EFS Web Filed
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Examiner Toth:

I, Ivo Drury, M.D., hereby declare and state, under penalty of perjury, that:

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Dated: Jan 12 2011

Ivo Drury, M.D.

PATENT
Attorney Docket No. **UM-09752**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Serial No.:	10/527,781	Group No.:	3735
Filed:	03/31/2006	Examiner:	Toth
Entitled:	**Noninvasive Nonlinear Systems and Methods for Predicting Seizure**		

DECLARATION OF Dingzhou Li UNDER 37 C.F.R. § 1.131

EFS Web Filed
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Examiner Toth:

I, Dingzhou Li, hereby declare and state, under penalty of perjury, that:

1. I am an inventor of the above-named patent application (hereinafter "present application").

2. In the Office Action dated August 2, 2010, the Examiner cited U.S. Patent Application Serial No. 2004/0122335 (hereinafter, "the Sackerelles patent application") which I understand has a filing date of August 23, 2003 and a priority claim based on a provisional patent application filed August 27, 2002 (U.S. Provisional Patent Application Serial No. 60/406,063 – hereinafter, "the Sackerelles provisional patent application").

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Dated: 1/13/11

Dingzhou Li

PATENT
Attorney Docket No. **UM-09752**

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Serial No.:	10/527,781	Group No.:	3735
Filed:	03/31/2006	Examiner:	Toth
Entitled:	**Noninvasive Nonlinear Systems and Methods for Predicting Seizure**		

DECLARATION OF Weiping Zhou UNDER 37 C.F.R. § 1.131

EFS Web Filed
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Examiner Toth:

I, Weiping Zhou, hereby declare and state, under penalty of perjury, that:

1. I am an inventor of the above-named patent application (hereinafter "present application").

2. In the Office Action dated August 2, 2010, the Examiner cited U.S. Patent Application Serial No. 2004/0122335 (hereinafter, "the Sackerelles patent application") which I understand has a filing date of August 23, 2003 and a priority claim based on a provisional patent application filed August 27, 2002 (U.S. Provisional Patent Application Serial No. 60/406,063 – hereinafter, "the Sackerelles provisional patent application").

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Dated: Jan 13, 2011

Weiping Zhou

Weiping Zhou

TAB B

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Non-linear, non-invasive method for seizure anticipation in focal epilepsy

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Abstract

In this paper we discuss an approach, using methods of non-linear time series analysis applied to scalp electrode recordings, which is able to distinguish between epochs temporally distant from and just prior to, the onset of a seizure in patients with temporal lobe epilepsy. The method involves a comparison of recordings taken from electrodes adjacent to and remote from the site of ictal onset. In particular, we define a non-linear quantity which we call 'marginal predictability'. This quantity is computed using data from remote and from adjacent electrodes. We find that the difference between the marginal predictabilities computed for the remote and adjacent electrodes decreases several tens of minutes prior to seizure onset, compared to its value interictally.

Keywords: Epilepsy; Seizure; Seizure prediction; Non-linear; Non-linear dynamics; Non-linear time series analysis

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1. Introduction

1.1. About epilepsy

Broadly speaking, there are two types of epilepsy, focal and generalized. In focal epilepsies there is thought to be a specific region of the brain from which the seizures originate (although, as we shall discuss below, this notion is vague and the reality may be considerably more complex). The most common type of focal epilepsy is temporal lobe epilepsy (TLE), in which the region of ictal (seizure) onset is in one (rarely both) of the temporal lobes. Generalized epilepsies are those in which there is no clearly identifiable site of ictal onset. Epilepsy affects about 2.5 million individuals in the US at any point in time, with about 150 000–200 000 new cases diagnosed per year [4]. Of all epilepsies, about 50% are focal epilepsies, and of these roughly 70% are epilepsies of the temporal lobe. Of patients with focal epilepsy, roughly 25% suffer a medically refractory condition, so that the only possible treatment currently available to them that might result in control of their seizures, is surgical resection of part of the temporal lobe. For these patients, in particular, a reliable ambulatory method of seizure anticipation would be a great boon. At the least, it would allow the patient to position himself in a safe environment (e.g. not driving, away from machinery, etc.) to weather the seizure. But being able to reliably anticipate seizure onset by at least several minutes could also open the door to the development of other protocols (short term medical or electrical interventions) that might successfully abort the seizure. Thus, the search for a reliable method of seizure anticipation has been a vigorous one for many years.

1.2. Non-linear dynamics and seizure anticipation

The first attempts at anticipating seizures naturally relied on standard linear statistical methods (see, for example [9,19]). Following the renaissance of non-linear dynamics and the realization that many natural processes embodied non-linearities in their dynamics, researchers in a variety of fields began looking for evidence of non-linearities, and specifically chaos in a wide range of data sets. Brain studies, and specifically EEG was no exception (see for example [3,8,27], and the articles in [7]). The hope was that observing chaos in biological systems could first, help elucidate the underlying dynamics of various biological processes and second, could lead to new methods of predicting potential deleterious events (e.g. sudden cardiac death, epileptic seizures) and to new methods of treating a variety of diseases. Early attempts met with mixed results, (for example, [3,6,12,20,26,27]). But a growing understanding in the biological community of the nature of chaos, and of the probable nature of non-linearities in many biological systems, led researchers to a more sophisticated view of the role of non-linear dynamics in their systems of interest. In studies of EEG, there is now a generally accepted understanding that low dimensional chaos per se is not likely to be manifest in most EEG data sets [26]. This understanding has led to a considerably more sophisticated view of non-linearities in EEG and to the development of methods of detecting such effects. In particular, work over the past 5 years or so by several groups (see, for example, [1,2,5,13,16,18,21,24,25]) has focused on a variety of non-linear measures, most (but not all) of which are based on correlation integrals [10]. Unlike previous work, these more recent investigations do not claim to detect chaos in EEG. Rather many groups take an empirical approach to their work, seeking to correlate values of non-linear measures with disease states either in space or time.

Most of the work has concentrated on the analysis of intracranial recordings. Intracranial recordings have traditionally been available from a subset of epilepsy patients with medically refractory temporal lobe epilepsy [11]. In cases in which patients are candidates for surgical resection of the seizure focus, and in which the location of the focus cannot be determined accurately enough using non-invasive methods, patients may undergo placement of intracranial electrodes. Such recordings, unlike scalp EEG do not suffer from muscle noise or attenuation of the signal by bone and tissue. They are therefore very attractive data sets to study for the presence of non-linear effects. Over the long term, however, intracranial studies have two important limitations. First, as non-invasive methods of determining seizure focus improved, the number of intracranial studies decreased limiting the available data base. Second, one important goal of the larger program of non-linear epilepsy studies is to develop ambulatory monitoring methods with a view to being able to anticipate seizures. Clearly, an ambulatory monitor that relies on recordings from scalp electrodes is likely to be much more easily tolerated and maintained than one that relies on implanted intracranial devices.

For these reasons, we have concentrated most of our efforts on the non-linear analysis of scalp EEG (although we have done some intracranial studies). This raises the bar of difficulty considerably, but also raises the significance of positive outcomes. As we will describe in the next section, we have been able to find a very interesting indicator of seizure onset that has strong statistical support. In the next section we will describe the mathematical basis of our method and we will also briefly describe the subject population used in our study. In Section 3 we will present our results. In that section we will describe both aggregate results in which we look at a pool of seizures from several patients, as well as results from individual patients. We will also briefly describe the statistical methods we use. The paper ends with a discussion and conclusions in Section 4.

2. Methods

2.1. Mathematical considerations

In this section, we describe the mathematical methods we have used in this analysis. The basis for many non-linear dynamical analyses is the correlation integral [10] defined as

$$C_d(y(i), y(j)) = P(\|y^{(d)}(i) - y^{(d)}(j)\| < \varepsilon), \tag{1}$$

where $P(\cdot)$ denotes the probability of the argument, x_j is the jth element of the time series being reconstructed, and $y^{(d)}(i) = (x_i, x_{i-1}, \ldots, x_{i-d+1})$ is a d-dimensional vector reconstructed from data. The notation $\|\cdot\|$ means norm of the argument. There are a number of different definitions that can be used for the norm. Although there are good theoretical and/or computational reasons for choosing one definition over the other, in practice (in most cases), the results of calculations differ little from one definition to the other. In our case we have chosen the max norm, which is computationally simplest, i.e. $\|y^{(d)}(i) - y^{(d)}(j)\| < \varepsilon$ if $\max[|x_{i-k} - x_{j-k}|] < \varepsilon$ for $k = 0, 1, \ldots, d-1$.

The quantity C_d is the probability that two vectors reconstructed from the time series in d-dimensions will be close to each other. In terms of the original time series, C_d is a measure of the likelihood that two sequences of length d taken from a time series will look similar.

Using the C_d's, we can define the predictability [23] as

$$S_d = \frac{C_{d+1}}{C_d}. \tag{2}$$

Using (1), it is not difficult to see that S_d is just the conditional probability

$$S_d = P(z_{d+1}|z_d, \ldots, z_1), \tag{3}$$

where

$$z_k = |x_{i+k-1} - x_{j+k-1}| < \varepsilon. \tag{4}$$

In words, S_d is just the conditional probability that if two randomly chosen d-tuples from the time series have their first $d-1$ elements within ε of each other, respectively, then the dth elements will also be within ε.

Although we could use the S_d as a non-linear statistic, we have found [17] that a more sensitive discriminator of non-linear structure in time series is the ratio of S_ds, defined as

$$R_d = \frac{S_d}{S_{d-1}} = \frac{C_{d+1}C_{d-1}}{C_d^2}. \tag{5}$$

To make the interpretation simple, we define the marginal predictability as

$$\delta_d \equiv \frac{R_d - 1}{R_d} \tag{6}$$

δ_d is a measure of how much additional predictive information there is in the $(d+1)$st lag of the time series, given that we have already used information in the intervening d lags. If δ_d is close to zero, then there is no additional predictive information, on average, for the current value of the time series in the value of the $(d+1)$st lag. If δ_d is significantly different from zero, then $S_d > S_{d-1}$, and there is additional predictive information in the $(d+1)$st lag. 'Predictive information' here must be understood in the sense of non-linear dynamics (see [23,30] for more details). Note also that δ_d is defined as a distribution over a data set or a window of data. As we shall explain in Section 3, we shall be interested in the variation of δ_d from one window to the next, but δ_d should not be understood as a function of time within a window.

Our approach has been to compare δ_d for two different scalp electrodes as a function of time. Thus, consider $Q_d(A, B; t) = \delta_d(A; t) - \delta_d(B; t)$, where A and B are two electrodes and t is time. Typically, A will be an electrode near the seizure focus and B will be an electrode remote from and ipsilateral to the site of ictal onset. In the case of TLE, B will generally be an occipital electrode. Thus we are interested in whether there is any difference in the marginal predictabilities of temporal and occipital electrodes between times far removed from a seizure and times close to a seizure. We have also compared these results to similar calculations (i) letting A and B be contralateral temporal and occipital electrodes, respectively and (ii) letting A and B be temporal ipsilateral and contralateral electrodes, respectively. In both these cases, Q_2 has, qualitatively, the same behavior as in the case in which A and B are both ipsilateral to the site of ictal onset. Detailed comparisons will be discussed elsewhere. In addition we have computed results from data taken from non-epileptics. As we shall discuss, results for non-epileptics are markedly different from those for epileptics.

2.2. Subject selection

Patients were evaluated by one of the authors (ID), or one of three other epileptologists at Henry Ford Hospital in Detroit. Presurgical evaluation at Henry Ford Hospital follows a standardized protocol [29] similar to such assessments at most major epilepsy centers.

In an effort to provide as homogenous and therefore comparable a group of patients as possible, we have limited our analysis to patients with medically refractory mesiobasal temporal lobe epilepsy, the most common patient group considered as suitable candidates for epilepsy surgery. The specific criteria for inclusion in our analysis are

Seizures had to be of unilateral mesiobasal temporal lobe origin, documented by history, interictal and ictal EEG recordings (see below for definition of interictal). Age between 18 and 60 years. This reduces the likelihood of age related disorders such as cerebrovascular disease.
No mass lesion detected with magnetic resonance imaging.
Intelligence quotient of 70 or more.
No evidence of a progressive neurological disorder, active neurological disorder other than epilepsy, and no other significant medical disorder, severe depression or psychosis.
No evidence of damage to the hippocampus contralateral to the seizure focus as determined by magnetic resonance imaging.
No history of drug or alcohol abuse.
Patients receiving barbiturates or benzodiazepines were excluded with the exception of intravenous benzodiazepines used for acute seizure control.
No history of drug use other than antiepileptic drugs during the two weeks prior to the recordings.

All EEG recordings were reviewed by one of the authors (ID) who is an experienced epileptologist and clinical neurophysiologist. EEG recordings from the patients were visually inspected to identify epochs of interest for analysis. Epochs were divided into the following sets: (1) interictal, meaning at least 1 h before and at least 1 h after a seizure; (2) preictal, meaning within the hour preceding a seizure, and at least 1 h following a seizure; and (3) ictal. Epochs were separated by behavioral state into wakefulness, drowsiness, stage 2 non-REM sleep, slow wave sleep and REM sleep. Waking and sleeping EEG from normal age and sex-matched subjects were also analyzed. All of these subjects underwent a complete medical and neurological history and comprehensive neurological examination by one of the authors (ID). Normal subjects had no history of drug and alcohol abuse, and had not used any medications in the two weeks prior to the study.

EEG recordings are recorded on a 128-channnel BMSI/Nicolet 5000 System. The band pass is 0.5–100 Hz. The digital data is then transferred to a Unix workstation for conversion to ASCII text data and further analysis.

3. Results

For the results presented here, 40 second windows, comprising 8000 data points (sampling rate of 200 Hz), are used to calculate each value of δ_d and $Q_d(A,B;t)$. The choice of a 40 second

window represents a compromise between the necessities for a reasonable amount of data for a good estimate of the δ_d and a short enough time so that the window can reasonably be associated with some single biological state. The time series x_i is obtained from the originally sampled (200 Hz) EEG recordings by using every third data point, thus resulting in a data set effectively representing a sampling rate of 67 Hz. This decimation of the data set was chosen to minimize the value of the mutual information [28]. ε in (4) is 10% of the standard deviation of the time series, x_i. This choice of ε is a compromise between the requirements of a significant amount of data, on the one hand and the desire to have the results be discriminative of different states. The choice of ε as 10% of the standard deviation is also consistent with a large literature in non-linear time series analysis in which similar choices for ε have been made. In the results presented here, $d = 2$. (Note that with $d = 2$ we actually use results from reconstructions in three dimensions.) The smaller d is, the more effectively the available data can be used. On the other hand, the larger d is, the more details of the dynamics can be revealed. We have found that $d = 2$ is large enough to provide us with sufficient detail for our purposes. We also note that moderate variations in our choices for the values of the window length, ε, and the decimation rate give results qualitatively similar to those we will present here. Thus, our approach does not require very finely tuned parameter choices. The results here include twenty-four 20 min preictal epochs from eight patients and 40 interictal epochs of 20 min duration from eight patients in the analysis. In both the interictal and preictal sets, the subject was awake for roughly 2/3 of the epochs and asleep during 1/3 of the epochs. As we shall mention below, we have also analyzed data for the asleep and awake epochs separately. Qualitatively, our results are independent of the behavior states. For purposes of comparison, we have also analyzed 24 epochs of 20 min duration from six non-epileptic subjects using the same methods.

In Fig. 1 we present a schematic diagram which indicates the standard nomenclature and placement of scalp electrodes according to the International 10–20 System. This figure shows the left side of the head. Electrodes placed in homologous locations on the right side of the scalp are labeled with the next highest even number. So, for example, the electrode on the right side of the head in the position homologous to the F7 electrode is labeled F8. Depending on the side of the seizure focus, the F7 or F8 electrode is typically close to the site of ictal onset in cases of TLE. Two examples of δ_2 as a function of time are shown in Figs. 2 and 3. Fig. 2(a) is the time course of δ_2 for a temporal electrode (F8) ipsilateral to the side of ictal onset during a 20 min interictal period. Fig. 2(b) is δ_2 for the occipital (O2) electrode ipsilateral to the side of ictal onset during the same period. Note that the δ_2(F8) is significantly higher than the δ_2(O2). Fig. 3(a) shows δ_2 for the same electrode (F8) used in Fig. 2(a), but calculated during a 1 h preictal period leading up to a seizure, and Fig. 3(b) shows δ_2 for the electrode (O2) used in Fig. 2(b), calculated during the same 1 h preictal period used for Fig. 2(a). Note that δ_2(F8) is still greater than δ_2(O2) until about 15 min before the seizure onset. Within 15 min prior to the seizure, however, δ_2(F8) decreases to approximately the same level as δ_2(O2).

It is easier to illustrate our findings by considering Q_2, which is the difference between the δ_2's of different electrodes. The results are presented in Fig. 4. Note that in Fig. 4(a) Q_2 is greater than zero for the interictal epoch (typically close to 0.05). For most of the early portion of the preictal epoch Q_2 is also greater than zero in Fig. 4(b), but moves close to and stays near zero starting about 15 min prior to the seizure. Although there are differences in the profiles of the δ_2's for different epochs, the features illustrated in Fig. 4, namely, the fact that Q_2 is smaller in the preictal

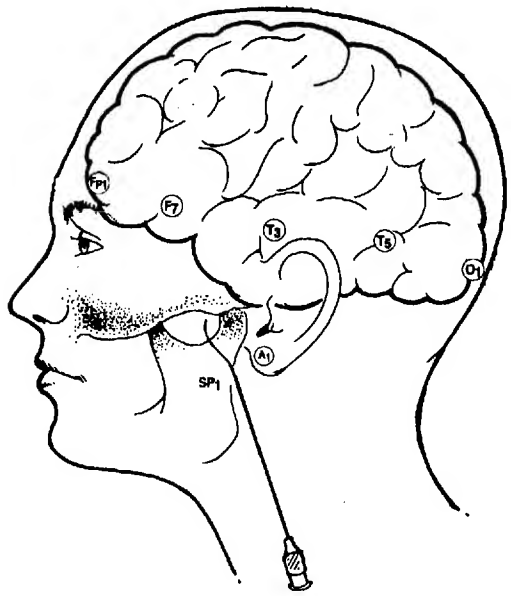

Fig. 1. Schematic representation of some of the standard scalp (International 10–20 System) and sphenoidal electrode coverage over the left hemisphere. Right hemisphere electrodes match those displayed here, but have the next highest even number. (Figure adapted from [29], with permission of the publisher.)

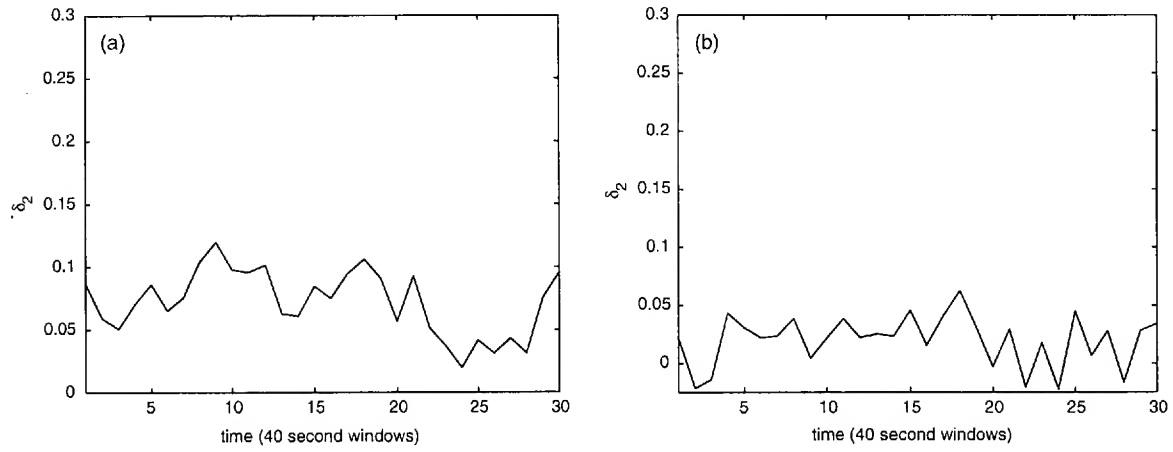

Fig. 2. (a) δ_2 as a function of time for a temporal electrode (F8) ipsilateral to the side of ictal onset during a 20 min interictal period. (b) δ_2 as a function of time for the occipital (O2) electrode ipsilateral to the side of ictal onset during the same period as in (a).

compared to the interictal period can be found in almost all of the epochs studied from the epileptic subjects (see below for a statistical analysis).

The same analysis was also applied to a set of epochs taken from non-epileptic subjects. Fig. 5 is an example of a 20 min epoch from a non-epileptic subject. The electrodes of interest here are a

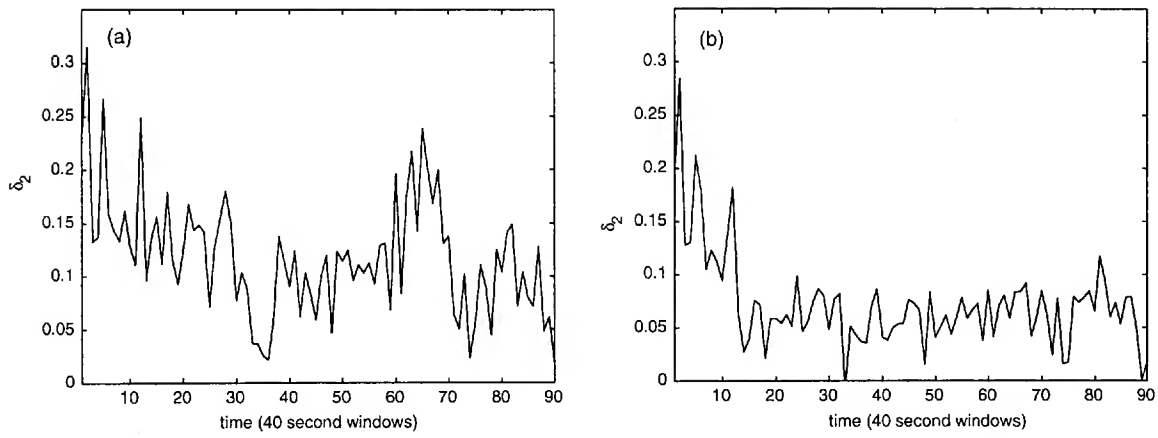

Fig. 3. (a) δ_2 as a function of time for a temporal electrode (F8) ipsilateral to the side of ictal onset during a 1 h preictal period leading up to a seizure. (b) δ_2 as a function of time for the occipital (O2) electrode ipsilateral to the side of ictal onset during the same period as in (a).

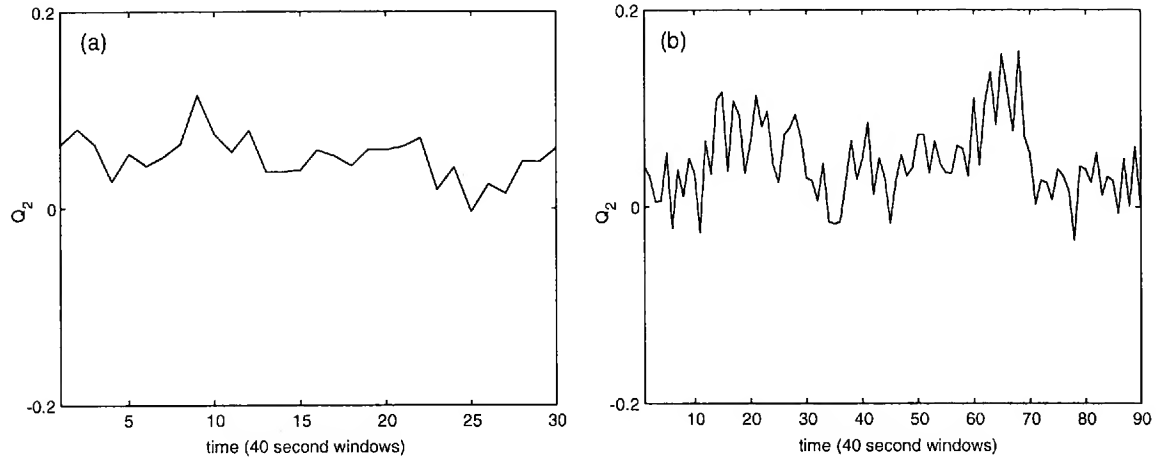

Fig. 4. (a) Q_2 as a function of time during the same period as in Fig. 2(a). (b) Q_2 as a function of time during the same period as in Fig. 3(a).

temporal electrode (F7) and an occipital electrode (O1), both on the left hemisphere. As can be seen from Fig. 5(c), the value of Q_2 for non-epileptic subjects are typically close to zero, which suggests that there is no systematic difference between the δ_2 of temporal electrodes and that of occipital electrodes for non-epileptic subjects.

In order to statistically validate these observations, a Wilcoxon's sum of signed rank test was applied to the values of Q_2. (See the Appendix A for a brief review of this statistical test.) Specifically, we performed summed-rank tests to test the null hypothesis that the median of δ_2 of the electrode adjacent to seizure onset, μ_{adj} (in our case, F7 or F8, depending on which side of the brain contained the site of ictal onset), is the same as that of the electrode remote to the site of seizure onset μ_{remote} (in this case the occipital electrode O1 or O2 ipsilateral to the site of ictal

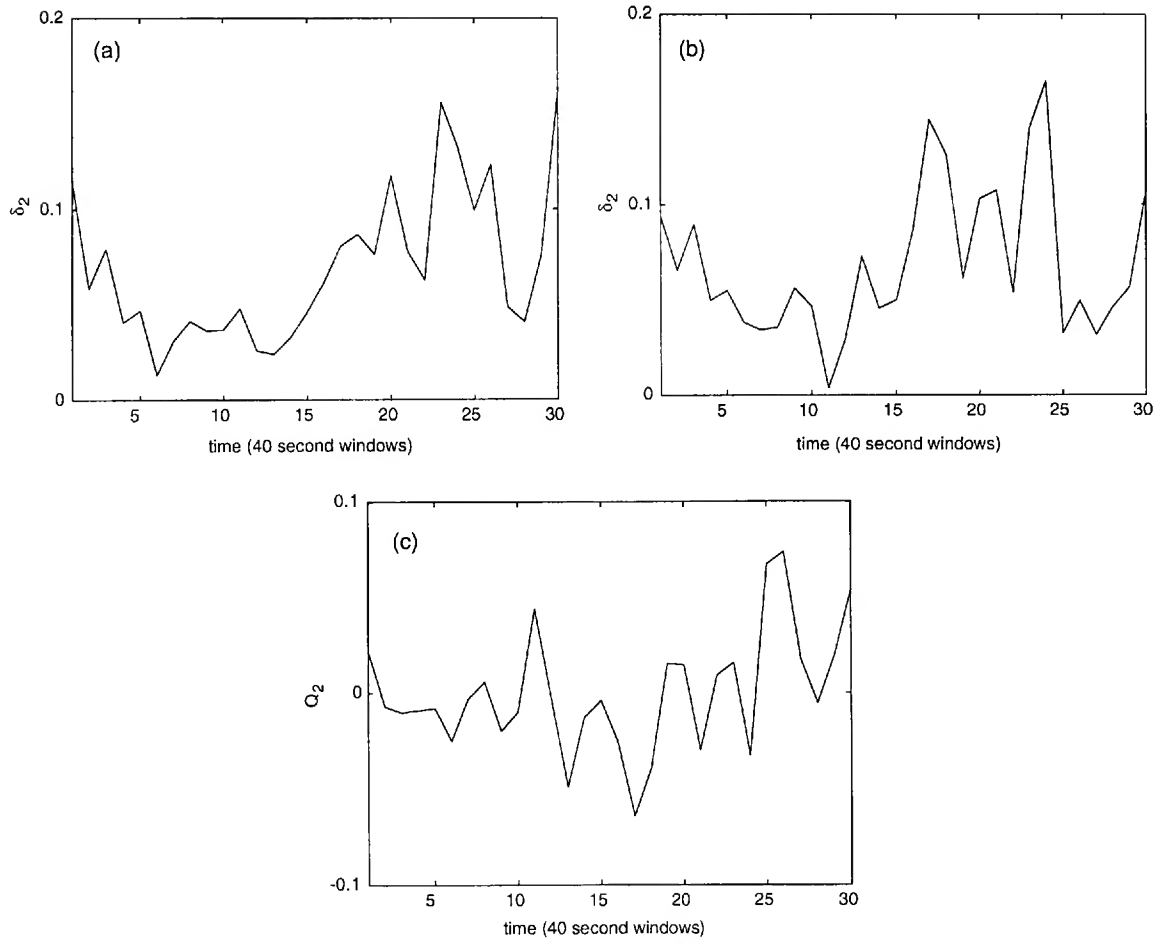

Fig. 5. (a) δ_2 as a function of time for a temporal electrode (F7) of a non-epileptic subject during a 20 min period. (b) δ_2 as a function of time for the occipital electrode (O1) of a non-epileptic subject during the same period as in (a). (c) Q_2 as a function of time during the same period as in (a).

onset), which means that $Q_2 = 0$, statistically. The sum of positive ranks (SPR) as a function of time are shown in Figs. 6–8 for interictal, preictal and non-epileptic subjects, respectively. If SPR is close to the average under the null hypothesis (the broken line in the middle of the graph), then we cannot reject the null hypothesis. However, if SPR, is too low, we must reject the null hypothesis and accept the alternative hypothesis that $\mu_{\text{adj}} > \mu_{\text{remote}}$ (i.e. $Q_2 > 0$). Fig. 6 shows the SPR for a collection of 40 interictal epochs of 20 min duration taken from eight patients with TLE. Each point represents one 40 second window. Fig. 7 is the SPR test for 24 one hour preictal epochs prior to seizure onset from this same cohort of patients, and Fig. 8 is the SPR for 24 epochs of 20 min duration taken from six non-epileptic subjects.

From Fig. 6 we see that we must reject the null hypothesis that the δ_2s are the same for the adjacent and remote electrodes interictally and accept the alternative hypothesis $Q_2 > 0$. In Fig. 7 we see that up to about 40 min prior to seizure onset, the δ_2s for the adjacent electrodes are

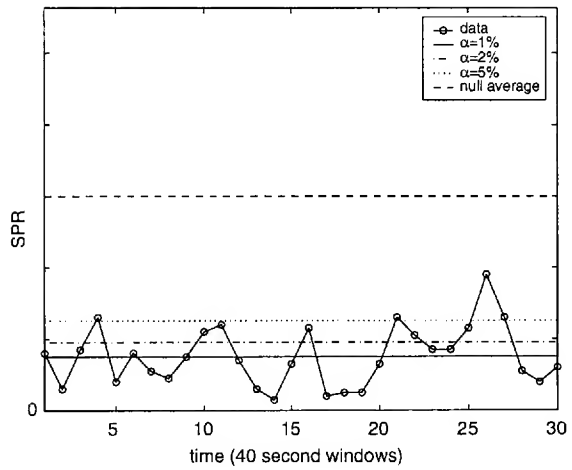

Fig. 6. The sum of positive ranks (SPR) for a collection of 40 interictal epochs of 20 min duration taken from eight patients with TLE.

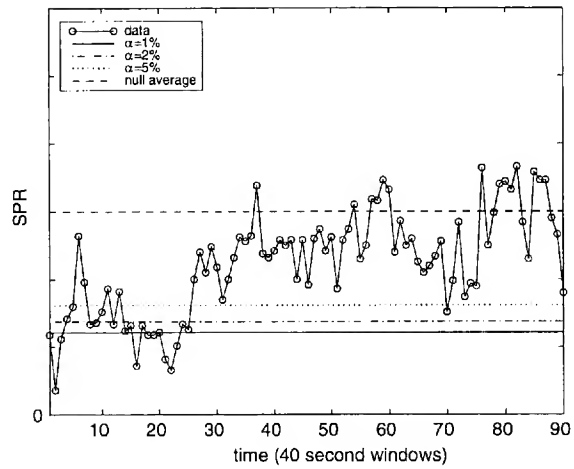

Fig. 7. The SPR test for 24 one hour preictal epochs prior to seizure onset from the same cohort of patients as in Fig. 6.

significantly greater than those for the ipsilateral remote electrodes and the null hypothesis is below 5% significance level over that time period. Within about 40 min prior to seizure onset, the SPR increases making rejection of the null hypothesis no longer possible. In words, the marginal predictability of the electrodes adjacent to the site of ictal onset is significantly greater than that of the ipsilateral occipital electrodes, except within about half an hour prior to a seizure, at which time the marginal predictabilities take on similar values. We have also performed similar analyses comparing sphenoidal and occipital scalp electrodes. The sphenoidal electrodes are also relatively close to the site of ictal onset in TLE. The results are qualitatively similar to those in Figs. 5 and 6, but are somewhat less distinct, probably due to increased noise and artifact from the sphenoidal electrodes. By comparison, in Fig. 8 we present the summed-rank test for epochs derived from

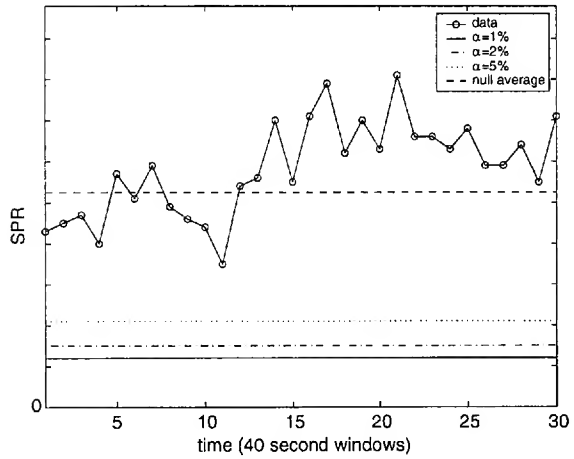

Fig. 8. The SPR for 24 epochs of 20 min duration taken from six non-epileptic subjects.

non-epileptic subjects. In marked contrast to the interictal epochs in patients with epilepsy, we see that for non-epileptic subjects we cannot reject the null hypothesis, and the δ_2s for the ipsilateral temporal and occipital electrodes are statistically the same. Finally we would like to point out that the statistical results are not related to the behavior state of the epochs in the set. We have run the test on the subsets of the preictal set and the interictal data for which the subjects were asleep during all the epochs. Qualitatively, our conclusions were unchanged.

These statistical results are very suggestive, but the real value of this approach lies in whether or not results are consistent across seizures within individual patients. We have also, therefore, been studying results patient by patient. Our preliminary results indicate that the aggregate results described in the previous paragraphs are nicely echoed in the disaggregated results on individual patients. For example, in Fig. 9 we show the values of Q_2 for four interictal and three preictal

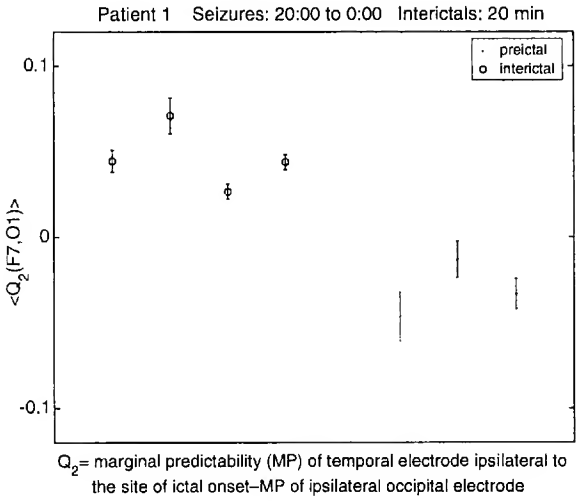

Fig. 9. Q_2 for four interictal and three preictal epochs for one patient.

epochs for one patient. It is clear that there is a systematic difference between the values of Q_2 obtained for interictal as opposed to preictal epochs. In fact, a survey of the individual results for the eight patients in this study reveals that, although for each given patient, Q_2 during the preictal epoch is not necessarily statistically zero, it is always smaller than the typical values of Q_2 during the interictal epochs for that patient. [1]

4. Discussion and conclusions

Our results strongly indicate a systematic change in a non-linear measure computed on scalp EEG recordings prior to ictal onset in patients with medically refractory temporal lobe epilepsy. There are several points to make about this observation.

First, any method of seizure anticipation assumes, a fortiori, that a seizure is not just a sudden catastrophic event, but that there are electrochemical changes that occur prior to the electrographic and clinical onset of the seizure. Indeed, there is strong anecdotal evidence that some patients experience prodromes of various kinds that precede seizure onset [22]. A seizure is a state in which neurons are pathologically synchronized in their firing. Presumably, therefore, prior to seizure onset, the brain enters a state in which the process of recruitment of neurons into a state of pathological synchrony is facilitated. In principle, there are many ways in which one can imagine this happening. There has been some speculation, based largely on observations from intracranial recordings that, prior to seizure onset, the brain, in the region near the ictal onset zone, passes through a state of decreased complexity, thereby facilitating the onset of pathological synchrony (see, for example, [15]). Despite these speculations, it is clear that the process of neuronal recruitment (and whether indeed it is a homogeneous process, or whether there are different dynamical processes that vary from patient to patient and seizure to seizure) is very poorly understood.

The studies reported in this paper differ methodologically from most other work in this field in two ways. First, we rely on data from scalp rather than intracranial recordings, and second, our indicators involve direct comparisons between data from scalp recordings adjacent to and remote from the ictal onset zone. It is interesting that δ_2 is approximately the same between temporal and occipital electrodes in normal subjects, as compared to its distinct behavior in interictal and preictal epochs in epileptics. While it is unclear what the detailed dynamical implications of these observations are, they do suggest the following conclusions: first, the systematic differences between interictal and preictal epochs of Q_2 in epileptics give credence to the notion that there is a recruitment process that takes place several tens of minutes prior to a seizure. Second, the fact that δ_2 in normals is about the same between occipital and focal electrodes, but is not the same interictally in epileptics suggests that there is an underlying persistent difference in the dynamics of the epileptic brain that may predispose it to the neuronal recruitment process that then gives rise

[1] Note that the fact that Q_2 preictally is smaller than Q_2 interictally on individual patients is not inconsistent with the conclusions from the SPR test for the aggregate. The point is that the condition $Q_2(\text{preictal}) < Q_2(\text{interictal})$ may be a more precise hypothesis for individual patients, but if there is a general bias in the aggregate for the median of $Q_2(\text{interictal})$ to be positive, then the SPR test for the aggregate could still reject the null hypothesis that $Q_2(\text{preictal}) = Q_2(\text{interictal})$ while at the same time indicating an aggregate statistical trend for $Q_2(\text{preictal})$ to be closer to zero.

to a seizure. Finally, it is interesting to note that, although there is consistency in the behavior of Q_2 between interictal and preictal epochs (Q_2(preictal) < Q_2(interictal)), the way in which the δ_2s for occipital and temporal electrodes behave varies from seizure to seizure. This also suggests that while there may be a neuronal recruitment process that gives rise to most seizures in patients with this syndrome, the way in which this process proceeds dynamically may be quite different from one seizure to the next.

Despite these lacunae in our understanding of the process of ictal onset the methods described here have significant potential for being the basis of a non-invasive, ambulatory method of seizure anticipation.

Acknowledgements

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Appendix A. The Wilcoxon signed rank test

The Wilcoxon test (see, for example, [14]) is a non-parametric test for paired samples (X_i, Y_i) (in this paper the paired samples are the marginal predictabilities for focal electrodes and remote electrodes, respectively, i.e. $(X_i, Y_i) = (\delta_2(\text{F electrodes}), \delta_2(\text{O electrodes}))$. It can be used to test the null hypothesis that the median of the difference, $D_i = X_i - Y_i$, is equal to zero, so that it is just as likely that $X_i > Y_i$ as that $X_i < Y_i$. Specifically, the test is calculated in the following way:

1. Rank order the absolute values of the D_i from smallest to largest. Let R_i be the rank of $|D_i|$, for $i = 1, \ldots, n$.
2. Assign the sign of D_i to the rank of D_i.
3. Calculate SPR, the sum of all the positive ranks, i.e. the sum of all those ranks that are associated with a positive value of D_i.

If the above null hypothesis, namely that the median of the differences, D_i, is zero, is true, we expect about half the D_i to be positive and half negative, and SPR will be neither too large nor too small, being close to $n(n+1)/4$, where n is the sample size. A test statistic can therefore be developed based upon SPR. Under the null hypothesis, the expected value of SPR is equal to $n(n+1)/4$, which is indicated by the broken lines in Figs. 6–8. The probability of each distinct value of SPR under the null hypothesis may also be calculated, giving significance levels. For example, for $n = 24$, the probability that SPR is less than 81 under the null hypothesis is approximately 0.025. Hence if SPR turned out to be less than 81, then we can reject the null hypothesis with 97.5% confidence. (In other words, the probability that the null hypothesis is rejected when it is true is only 2.5%.)

The advantage of the Wilcoxon signed rank test over parametric tests (such as the t-test) is that it does not make any ancillary assumptions about the distribution of D_i. The only necessary assumption is that all D_i's are independently sampled from the same distribution.

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TAB C

Nonlinear, Non-invasive Method for Seizure Anticipation in Focal Epilepsy

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Abstract

In this paper we discuss an approach, using methods of nonlinear time series analysis applied to scalp electrode recordings, which is able to distinguish between epochs temporally distant from and just prior to, the onset of a seizure in patients with temporal lobe epilepsy. The method involves a comparison of recordings taken from electrodes adjacent to and remote from the site of ictal onset. In particular, we define a nonlinear quantity which we call "marginal predictability". This quantity is computed using data from remote and from adjacent electrodes. We find that the difference between the marginal predictabilities computed for the remote and adjacent electrodes decreases several tens of minutes prior to seizure onset, compared to its value interictally.

I. Introduction

A. About Epilepsy

Broadly speaking, there are two types of epilepsy, focal and generalized. In focal epilepsies there is thought to be a specific region of the brain from which the seizures originate (although, as we shall discuss below, this notion is vague and the reality may be considerably more complex). The most common type of focal epilepsy is temporal lobe epilepsy (TLE), in which the region of ictal (seizure) onset is in one (rarely both) of the temporal lobes. Generalized epilepsies are those in which there is no clearly identifiable site of ictal onset. Epilepsy affects about 2.5 million individuals in the US at any point in time, with about 150,000-200,000 new cases diagnosed per year. [Begley et al. (2000)]. Of all epilepsies, about 50% are focal epilepsies, and of these roughly 70% are epilepsies of the temporal lobe. Of patients with focal epilepsy, roughly 25% suffer a medically refractory condition, so that the only possible treatment currently available to them that might result in control of their seizures, is surgical resection of part of the temporal lobe. For these patients, in particular, a reliable ambulatory method of seizure anticipation would be a great boon. At the least, it would allow the patient to position himself in a safe environment (eg. not driving, away from machinery, etc.) to weather the seizure. But being able to reliably anticipate seizure onset by at least several minutes could also open the door to the development of other protocols (short term medical or electrical interventions) that might successfully abort the seizure. Thus, the search for a reliable method of seizure anticipation has been a vigorous one for many years.

B. Nonlinear Dynamics and Seizure Anticipation

The first attempts at anticipating seizures naturally relied on standard linear statistical methods. (See, for example [Gotman, *et al.* 1985, Osorio 1998].) Following the renaissance of nonlinear dynamics and the realization that many natural processes embodied nonlinearities in their dynamics, researchers in a variety of fields began looking for evidence of nonlinearities, and specifically chaos in a wide range of data sets. Brain studies, and specifically EEG was no exception. [See for example Theiler (1995), Babloyantz and Destexhe (1986), Frank *et al.* (1990), and the articles in Duke and Pritchard (1991)]. The hope was that observing chaos in biological systems could first, help elucidate the underlying dynamics of various biological processes and second, could lead to new methods of predicting potential deleterious events (eg. sudden cardiac death, epileptic seizures) and to new methods of treating a variety of diseases. Early attempts met with mixed results, [for example, Theiler (1995), Theiler and Rapp (1996), Palus (1994), Babloyantz and Destexhe (1986), Iasemides *et al.* (1990), Destexhe and Babloyantz (1991)]. But a growing understanding in the biological community of the nature of chaos, and of the probable nature of nonlinearities in many biological systems, led researchers to a more sophisticated view of the role of nonlinear dynamics in their systems of interest. In studies of EEG, there is now a generally accepted understanding that low dimensional chaos *per se* is not likely to be manifest in most EEG data sets [Theiler and Rapp (1996), Gribkov (2000)]. This understanding has led to a considerably more sophisticated view of nonlinearities in EEG and to the development of methods of detecting such effects. In particular, work over the past 5 years or so by several groups [see for example, Andrezjak, et al. (2001), Arnhold, et al. (1999), Casdagli, et al, (1996),

Drury, et al. (2002), Protopopescu (2001), Le Van Quyen, et al. (2001), Manuca, et al. (1998), Savit, et al. (2001), Jerger, et al. (2001)] has focused on a variety of nonlinear measures, most (but not all) of which are based on correlation integrals [Grassberger and Procaccia (1983)]. Unlike previous work, these more recent investigations do not claim to detect chaos in EEG. Rather many groups take an empirical approach to their work, seeking to correlate values of nonlinear measures with disease states either in space or time.

Most of the work has concentrated on the analysis of intracranial recordings. Intracranial recordings have traditionally been available from a subset of epilepsy patients with medically refractory temporal lobe epilepsy (TLE) [Henry and Ross (1992)]. In cases in which patients are candidates for surgical resection of the seizure focus, and in which the location of the focus cannot be determined accurately enough using non-invasive methods, patients may undergo placement of intracranial electrodes. Such recordings, unlike scalp EEG do not suffer from muscle noise or attenuation of the signal by bone and tissue. They are therefore very attractive data sets to study for the presence of nonlinear effects. Over the long term, however, intracranial studies have two important limitations. First, as noninvasive methods of determining seizure focus improved, the number of intracranial studies decreased limiting the available data base. Second, one important goal of the larger program of nonlinear epilepsy studies is to develop ambulatory monitoring methods with a view to being able to anticipate seizures. Clearly, an ambulatory monitor that relies on recordings from scalp electrodes is likely to be much more easily tolerated and maintained than one that relies on implanted intracranial devices.

For these reasons, we have concentrated most of our efforts on the nonlinear analysis of scalp EEG (although we have done some intracranial studies). This raises the bar of difficulty considerably, but also raises the significance of positive outcomes. As we will describe in the next section, we have been able to find a very interesting indicator of seizure onset that has strong statistical support. In the next section we will describe the mathematical basis of our method and we will also briefly describe the subject population used in our study. In Section III we will present our results. In that section we will describe both aggregate results in which we look at a pool of seizures from several patients, as well as results from individual patients. We will also briefly describe the statistical methods we use. The paper ends with a discussion and conclusions in Section IV.

II. Methods

A. Mathematical considerations

In this section, we describe the mathematical methods we have used in this analysis. The basis for many nonlinear dynamical analyses is the correlation integral [Grassberger and Procaccia (1983)] defined as

$$C_d(y(i), y(j)) = P(\|y^{(d)}(i) - y^{(d)}(j)\| < \varepsilon) \qquad (1)$$

where P(·) denotes the probability of the argument, x_j is the jth element of the time series being reconstructed, and $y^{(d)}(i) = (x_i, x_{i-1}, \ldots, x_{i-d+1})$ is a d-dimensional vector reconstructed from data. The notation $\| \cdot \|$ means norm of the argument. There are a number of different definitions that can be used for the norm. Although there are good theoretical and/or computational reasons for choosing one definition over the other, in practice (in most cases), the results of calculations differ little from one definition to the other. In our case we have chosen the max norm, which is computationally simplest, i.e., $\left\| y^{(d)}(i) - y^{(d)}(j) \right\| < \varepsilon$ if $\max[|x_{i-k} - x_{j-k}|] < \varepsilon$ for k=0, 1, ..,d-1.

The quantity C_d is the probability that two vectors reconstructed from the time series in d-dimensions will be close to each other. In terms of the original time series, C_d is a measure of the likelihood that two sequences of length d taken from a time series will look similar.

Using the C_d's, we can define the predictability [Savit and Green (1991)] as

$$S_d = \frac{C_{d+1}}{C_d}. \qquad (2)$$

Using (1), it is not difficult to see that S_d is just the conditional probability

$$S_d = P(z_{d+1} \mid z_d, \ldots, z_1) \qquad (3)$$

where

$$z_k = | x_{i+k-1} - x_{j+k-1} | < \varepsilon \qquad (4)$$

In words, S_d is just the conditional probability that if two randomly chosen d-tuples from the time series have their first d-1 elements within ε of each other, respectively, then the d^{th} elements will also be within ε.

Although we could use the S_d as a nonlinear statistic, we have found [Manuca and Savit (1996)] that a more sensitive discriminator of nonlinear structure in time series is the ratio of S_d's, defined as

$$R_d = \frac{S_d}{S_{d-1}} = \frac{C_{d+1} C_{d-1}}{C_d^2}. \qquad (5)$$

To make the interpretation simple, we define the marginal predictability as:

$$\delta_d \equiv \frac{R_d - 1}{R_d} \qquad (6)$$

δ_d is a measure of how much additional predictive information there is in the $(d+1)^{st}$ lag of the time series, given that we have already used information in the intervening d lags. If δ_d is close to zero, then there is no additional predictive information, on average, for the current value of the time series in the value of the $(d+1)^{st}$ lag. If δ_d is significantly different from zero, then $S_d > S_{d-1}$, and there is additional predictive information in the $(d+1)^{st}$ lag. "Predictive information" here must be understood in the sense of nonlinear dynamics. See [Savit and Green (1991), and Wu, et al. (1993)] for more details.

Our approach has been to compare δ_d for two different scalp electrodes as a function of time. Thus, consider $Q_d(A,B;t)= \delta_d (A;t)- \delta_d(B;t)$, where A and B are two electrodes and t is time. Typically, A will be an electrode near the seizure focus and B will be an electrode remote from and ipsilateral to the site of ictal onset. In the case of TLE, B will generally be an occipital electrode. Thus we are interested in whether there is any difference in the marginal predictabilities of temporal and occipital electodes between times far removed from a seizure and times close to a seizure. We have also compared these results to similar calculations i.) letting A and B be contralateral temporal and occipital electrodes, respectively and ii.) letting A and B be temporal ipsilateral and contralateral electrodes, respectively. In addition we have computed results from data taken from non-epileptics.

II Subject Selection

Patients were evaluated by one of the authors (ID), or one of three other epileptologists at Henry Ford Hospital in Detroit. Presurgical evaluation at Henry Ford Hospital follows a standardized protocol (Valachovic 1997) similar to such assessments at most major epilepsy centers.

In an effort to provide as homogenous and therefore comparable a group of patients as possible, we have limited our analysis to patients with medically refractory mesiobasal temporal lobe epilepsy, the most common patient group considered as suitable candidates for epilepsy surgery. The specific criteria for inclusion in our analysis are:

Seizures had to be of unilateral mesiobasal temporal lobe origin, documented by history, interictal and ictal EEG recordings (see below for definition of interictal). Age between 18 and 60 years. This reduces the likelihood of age related disorders such as cerebrovascular disease.

No mass lesion detected with magnetic resonance imaging.

Intelligence Quotient of 70 or more.

No evidence of a progressive neurological disorder, active neurological disorder other than epilepsy, and no other significant medical disorder, severe depression or psychosis.

No evidence of damage to the hippocampus contralateral to the seizure focus as determined by magnetic resonance imaging.

No history of drug or alcohol abuse.

Patients receiving barbiturates or benzodiazepines were excluded with the exception of intravenous benzodiazepines used for acute seizure control.

No history of drug use other than antiepileptic drugs during the two weeks prior to the recordings.

All EEG recordings were reviewed by one of the authors (ID) who is an experienced epileptologist and clinical neurophysiologist. EEG recordings from the patients were visually inspected to identify epochs of interest for analysis. Epochs were divided into the following sets: 1) interictal, meaning at least 1 hour before and at least one hour after a seizure, 2) preictal, meaning within the hour preceding a seizure, and at least 1 hour following a seizure, and 3) ictal. Epochs were separated by behavioral state into wakefulness, drowsiness, stage 2 Non-REM sleep, slow wave sleep and REM sleep. Waking and sleeping EEG from normal age and sex-matched subjects were also analyzed. All of these subjects underwent a complete medical and neurological history and comprehensive neurological examination by one of the authors (ID). Normal subjects had no history of drug and alcohol abuse, and had not used any medications in the two weeks prior to the study.

EEG recordings are recorded on a 128-channnel BMSI/Nicolet 5000 System. The band pass is .5 Hz to 100 Hz. The digital data is then transferred to a Unix workstation for conversion to ASCII text data and further analysis.

III. Results

For the results presented here, 40 second windows, comprising 8000 data points (sampling rate of 200 Hz), are used to calculate δ_d and $Q_d(A.B;t)$. The time series x_i is obtained from the originally sampled EEG recordings by using every third data point. This decimation of the data set was chosen to minimize the value of the mutual information [Tong (1990)]. ε in (4) is 10% of the standard deviation of the time series, x_i. In the results presented here, d=2. The results here include twenty-four 20 minute preictal epochs from eight patients and forty interictal epochs of 20 minute duration from eight patients in the analysis. In both the interictal and preictal sets, the subject was awake for roughly 2/3 of the epochs and asleep during 1/3 of the epochs. As we shall mention below, we have also analyzed data for the asleep and awake epochs separately. Qualitatively, our results are independent of the behavior states. For purposes of comparison, we have also analyzed twenty four epochs of 20 minute duration from six non-epileptic subjects using the same methods.

In Fig. 1 we present a schematic diagram which indicates the standard nomenclature and placement of scalp electrodes according to the International 10-20 System. This figure shows the left side of the head. Electrodes placed in homologous locations on the right side of the scalp are labeled with the next highest even number. So, for example, the electrode on the right side of the head in the position homologous to the F7 electrode is labeled F8. Depending on the side of the seizure focus, the F7 or F8 electrode is typically close to the site of ictal onset in cases of TLE. Two examples of δ_2 as a function of time are shown in Figs. 2 and 3. Fig. 2a is the time course of δ_2 for a temporal electrode (F8) ipsilateral to the side of ictal onset during a 20 minute interictal period. Fig. 2b is δ_2 for

the occipital (O2) electrode ipsilateral to the side of ictal onset during the same period. Note that the δ_2(F8) is significantly higher than the δ_2(O2). Fig. 3a shows δ_2 for the same electrode (F8) used in Fig. 2a, but calculated during a one hour preictal period leading up to a seizure, and Fig. 3b shows δ_2 for the electrode (O2) used in Fig. 2b, calculated during the same one hour preictal period used for Fig. 2a. Note that δ_2(F8) is still greater than δ_2(O2) until about 15 minutes before the seizure onset. Within 15 minutes prior to the seizure, however, δ_2(F8) decreases to approximately the same level as δ_2(O2).

It is easier to illustrate our findings by considering Q_2, which is the difference between the δ_2's of different electrodes. The results are presented in Figs. 4. Note that in Fig. 4a Q_2 is greater than zero for the interictal epoch (typically close to 0.05). For most of the early portion of the preictal epoch Q_2 is also greater than zero in Fig. 4b, but moves close to and stays near zero starting about 15 minutes prior to the seizure. Although there are differences in the profiles of the δ_2's for different epochs, the features illustrated in Fig. 4, namely, the fact that Q_2 is smaller in the preictal compared to the interictal period can be found in almost all of the epochs studied from the epileptic subjects (see below for a statistical analysis).

The same analysis was also applied to a set of epochs taken from non-epileptic subjects. Fig. 5 is an example of a 20 minute epoch from a non-epileptic subject. The electrodes of interest here are a temporal electrode (F7) and an occipital electrode (O1), both on the left hemisphere. As can be seen from Fig. 5c, the value of Q_2 for non-epileptic subjects are typically close to zero, which suggests that there is no systematic difference between the δ_2 of temporal electrodes and that of occipital electrodes for non-epileptic subjects.

In order to statistically validate these observations, a Wilcoxon's sum of signed rank test was applied to the values of Q_2. (See the Appendix for a brief review of this statistical test.) Specifically, we performed summed-rank tests to test the null hypothesis that the median of δ_2 of the electrode adjacent to seizure onset, μ_{adj} (in our case, F7 or F8, depending on which side of the brain contained the site of ictal onset), is the same as that of the electrode remote to the site of seizure onset μ_{remote} (in this case the occipital electrode O1 or O2 ipsilateral to the site of ictal onset), which means that Q_2=0, statistically. The sum of positive ranks (SPR) as a function of time are shown in Figs. 6, 7 and 8 for interictal, preictal and non-epileptic subjects, respectively. If SPR is close to the average under the null hypothesis (the broken line in the middle of the graph), then we cannot reject the null hypothesis. . However, if SPR, is too low, we must reject the null hypothesis and accept the alternative hypothesis that $\mu_{adj} > \mu_{remote}$ (i.e. $Q_2>0$). Fig. 6 shows the SPR for a collection of 40 interictal epochs of 20 minute duration taken from 8 patients with TLE. Each point represents one 40 second window. Fig. 7 is the SPR test for 24 one hour preictal epochs prior to seizure onset from this same cohort of patients, and Fig. 8 is the SPR for 24 epochs of 20 minute duration taken from 6 non-epileptic subjects.

From Fig. 6 we see that we must reject the null hypothesis that the δ_2's are the same for the adjacent and remote electrodes interictally and accept the alternative hypothesis $Q_2>0$. In Fig. 7 we see that up to about forty minutes prior to seizure onset, the δ_2's for the

adjacent electrodes are significantly greater than those for the ipsilateral remote gfranks@gotnet.netelectrodes and the null hypothesis is below 5% significance level over that time period. Within about 40 minutes prior to seizure onset, the SPR increases making rejection of the null hypothesis no longer possible. In words, the marginal predictability of the electrodes adjacent to the site of ictal onset is significantly greater than that of the ipsilateral occipital electrodes, except within about half an hour prior to a seizure, at which time the marginal predictabilities take on similar values. We have also performed similar analyses comparing sphenoidal and occipital scalp electrodes. The sphenoidal electrodes are also relatively close to the site of ictal onset in TLE. The results are qualitatively similar to those in Figs. 5 and 6, but are somewhat less distinct, probably due to increased noise and artifact from the sphenoidal electrodes. By comparison, in Fig. 8 we present the summed-rank test for epochs derived from non-epileptic subjects. In marked contrast to the interictal epochs in patients with epilepsy, we see that for non-epileptic subjects we cannot reject the null hypothesis, and the δ_2's for the ipsilateral temporal and occipital electrodes are statistically the same. Finally we would like to point out that the statistical results are not related to the behavior state of the epochs in the set. We have run the test on the subsets of the preictal set and the interictal data for which the subjects were asleep during all the epochs. Qualitatively, our conclusions were unchanged.

These statistical results are very suggestive, but the real value of this approach lies in whether or not results are consistent across seizures within individual patients. We have also, therefore, been studying results patient by patient. Our preliminary results indicate that the aggregate results described in the previous paragraphs are nicely echoed in the disaggregated results on individual patients. For example, in Fig. 9 we show the values of Q_2 for 4 interictal and 3 preictal epochs for one patient. It is clear that there is a systematic difference between the values of Q_2 obtained for interictal as opposed to preictal epochs. In fact, a survey of the individual results for the eight patients in this study reveals that, although for each given patient, Q_2 during the preictal epoch is not necessarily statistically zero, it is always smaller than the typical values of Q_2 during the interictal epochs for that patient.[1]

IV. Discussion and Conclusions

Our results strongly indicate a systematic change in a nonlinear measure computed on scalp EEG recordings prior to ictal onset in patients with medically refractory temporal lobe epilepsy. There are several points to make about this observation.

First, any method of seizure anticipation assumes, *a fortiori*, that a seizure is not just a sudden catastrophic event, but that there are electrochemical changes that occur prior to

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[1] Note that the fact that Q_2 preictally is smaller than Q_2 interictally on individual patients is not inconsistent with the conclusions from the SPR test for the aggregate. The point is that the condition $Q_2(\text{preictal}) < Q_2(\text{interictal})$ may be a more precise hypothesis for individual patients, but if there is a general bias in the aggregate for the median of Q_2(interictal) to be positive, then the SPR test for the aggregate could still reject the null hypothesis that $Q_2(\text{preictal}) = Q_2(\text{interictal})$ while at the same time indicating an aggregate statistical trend for Q_2(preictal) to be closer to zero.

the electrographic and clinical onset of the seizure. Indeed, there is strong anecdotal evidence that some patients experience prodromes of various kinds that precede seizure onset [Rajna *et al* 1997]. A seizure is a state in which neurons are pathologically synchronized in their firing. Presumably, therefore, prior to seizure onset, the brain enters a state in which the process of recruitment of neurons into a state of pathological synchrony is facilitated. In principle, there are many ways in which one can imagine this happening. There has been some speculation, based largely on observations from intracranial recordings that, prior to seizure onset, the brain, in the region near the ictal onset zone, passes through a state of decreased complexity, thereby facilitating the onset of pathological synchrony. (See, for example, [Lehnertz 2001]) Despite these speculations, it is clear that the process of neuronal recruitment (and whether indeed it is a homogeneous process, or whether there are different dynamical processes that vary from patient to patient and seizure to seizure) is very poorly understood.

The studies reported in this paper differ methodologically from most other work in this field in two ways. First, we rely on data from scalp rather than intracranial recordings, and second, our indicators involve direct comparisons between data from scalp recordings adjacent to and remote from the ictal onset zone. It is interesting that δ_2 is approximately the same between temporal and occipital electrodes in normal subjects, as compared to its distinct behavior in interictal and preictal epochs in epileptics. While it is unclear what the detailed dynamical implications of these observations are, they do suggest the following conclusions: First, the systematic differences between interictal and preictal epochs of Q_2 in epileptics gives credence to the notion that there is a recruitment process that takes place several tens of minutes prior to a seizure. Second, the fact that δ_2 in normals is about the same between occipital and focal electrodes, but is not the same interictally in epileptics suggests that there is an underlying persistent difference in the dynamics of the epileptic brain that may predispose it to the neuronal recruitment process that then gives rise to a seizure. Finally, it is interesting to note that, although there is consistency in the behavior of Q_2 between interictal and preictal epochs (Q_2(preictal)<Q_2(interictal)), the way in which the δ_2's for occipital and temporal electrodes behave varies from seizure to seizure. This also suggests that while there may be a neuronal recruitment process that gives rise to most seizures in patients with this syndrome, the way in which this process proceeds dynamically may be quite different from one seizure to the next.

Despite these lacunae in our understanding of the process of ictal onset the methods described here have significant potential for being the basis of a non-invasive, ambulatory method of seizure anticipation.

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Appendix: the Wilcoxon signed rank test

The Wilcoxon test (See, for example, [Lehmann 1975]) is a nonparametric test for paired samples (X_i, Y_i) (in this paper the paired samples are the marginal predictabilities for focal electrodes and remote electrodes, respectively, i.e. $(X_i, Y_i) = (\delta_2(\text{F electrodes}), \delta_2(\text{O electrodes}))$. It can be used to test the null hypothesis that the median of the difference, $D_i = X_i - Y_i$, is equal to zero, so that it is just as likely that $X_i > Y_i$ as that $X_i < Y_i$. Specifically, the test is calculated in the following way:

1. Rank order the absolute values of the D_i from smallest to largest. Let R_i be the rank of $|D_i|$, for $i = 1, \ldots, n$.
2. Assign the sign of D_i to the rank of D_i.
3. Calculate SPR, the sum of all the positive ranks, i.e., the sum of all those ranks that are associated with a positive value of D_i.

If the above null hypothesis, namely that the median of the differences, D_i, is zero, is true, we expect about half the D_i to be positive and half negative, and SPR will be neither tool large nor too small, being close to $n(n+1)/4$, where n is the sample size. A test statistic can therefore be developed based upon SPR. Under the null hypothesis, the expected value of SPR is equal to $n(n+1)/4$, which is indicated by the broken lines in the Figs. 6, 7, and 8. The probability of each distinct value of SPR under the null hypothesis may also be calculated, giving significance levels. For example, for $n = 24$, the probability that SPR is less than 81 under the null hypothesis is approximately 0.025. Hence if SPR turned out to be less than 81, then we can reject the null hypothesis with 97.5% confidence. (In other words, the probability that the null hypothesis is rejected when it is true is only 2.5%).

The advantage of the Wilcoxon signed rank test over parametric tests (such as the t-test) is that it does not make any ancillary assumptions about the distribution of D_i. The only necessary assumption is that all D_i's are independently sampled from the same distribution.

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Figure Captions

Fig. 1. Schematic representation of some of the standard scalp (International 10-20 System) and sphenoidal electrode coverage over the left hemisphere. Right hemisphere electrodes match those displayed here, but have the next highest even number.

Fig. 2a. δ_2 as a function of time for a temporal electrode (F8) ipsilateral to the side of ictal onset during a 20 minute interictal period.

Fig. 2b δ_2 as a function of time for the occipital (O2) electrode ipsilateral to the side of ictal onset during the same period as in Fig. 2a.

Fig. 3a. δ_2 as a function of time for a temporal electrode (F8) ipsilateral to the side of ictal onset during a one hour preictal period leading up to a seizure

Fig. 3b. δ_2 as a function of time for the occipital (O2) electrode ipsilateral to the side of ictal onset during the same period as in Fig. 3a.

Fig. 4a Q_2 as a function of time during the same period as in Fig. 2a.

Fig. 4b Q_2 as a function of time during the same period as in Fig. 3a.

Fig. 5a δ_2 as a function of time for a temporal electrode (F7) of a non-epileptic subject during a 20 minute period

Fig. 5b δ_2 as a function of time for the occipital electrode (O1) of a non-epileptic subject during the same period as in Fig. 5a.

Fig. 5c Q_2 as a function of time during the same period as in Fig. 5a.

Fig. 6 The sum of positive ranks (SPR) for a collection of 40 interictal epochs of 20 minute duration taken from 8 patients with TLE.

Fig. 7 The SPR test for 24 one hour preictal epochs prior to seizure onset from the same cohort of patients as in Fig. 6

Fig. 8 The SPR for 24 epochs of 20 minute duration taken from 6 non-epileptic subjects.

Fig. 9 Q_2 for 4 interictal and 3 preictal epochs for one patient

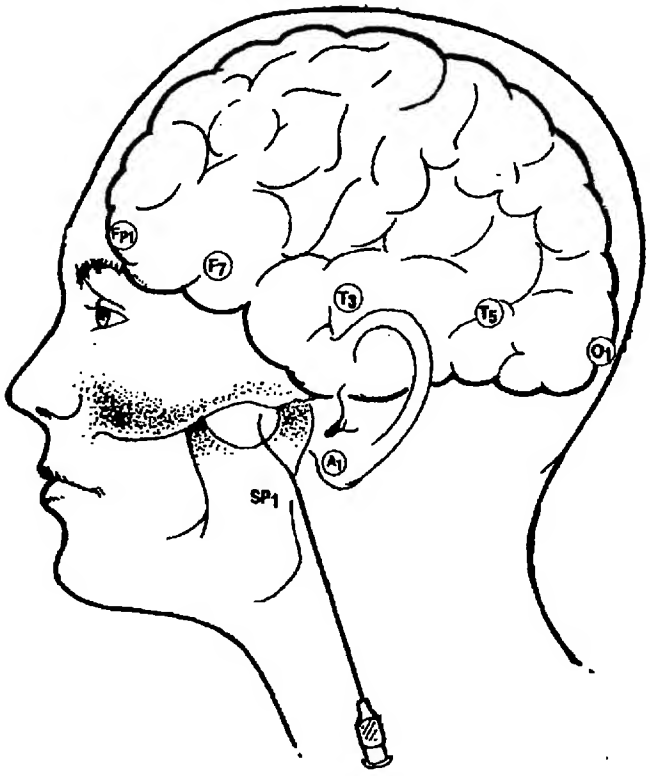

Figure 1

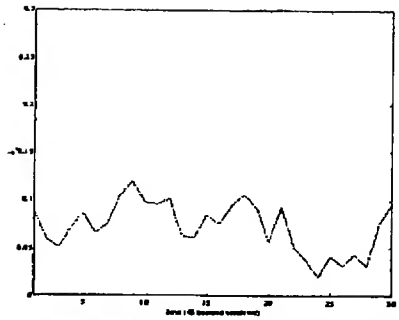

Figure 2a: interictal $\delta_2(t)$ for F8 (20 minute epoch)

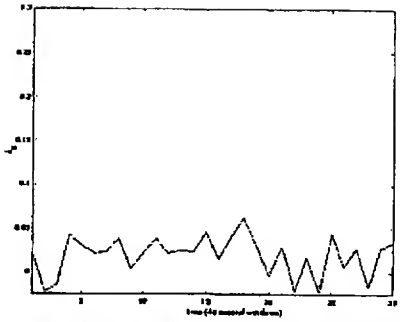

Figure 2b: interictal $\delta_2(t)$ for O2 (20 minute epoch)

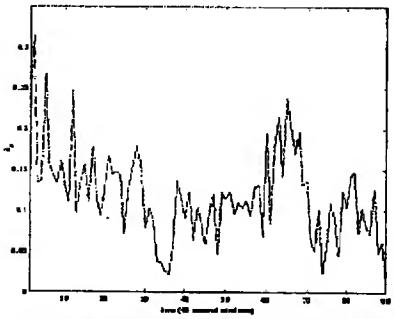

Figure 3a: preictal $\delta_2(t)$ for F8 (60 minute epoch)

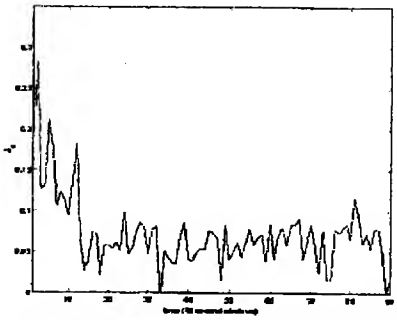

Figure 3b: preictal $\delta_2(t)$ for O2 (60 minute epoch)

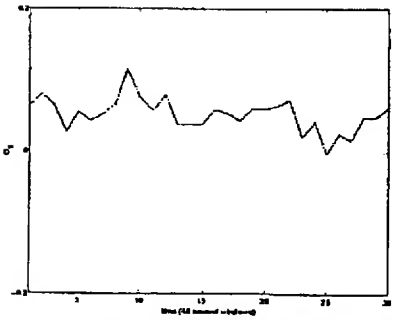

Figure 4a: interictal $Q_2(F8, O2; t)$ (20 minute epoch)

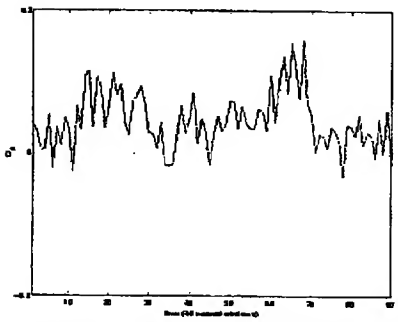

Figure 4b: preictal $Q_2(F8, O2; t)$ (60 minute epoch)

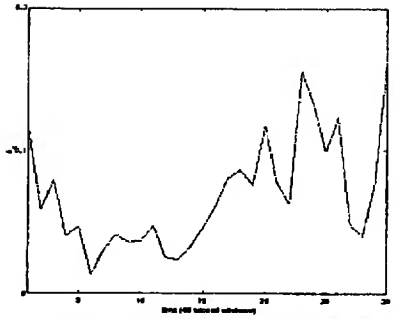

Figure 5a: $\delta_2(t)$ for F7 in non-epileptic subject (20 minute epoch)

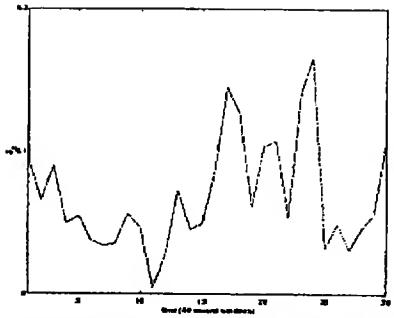

Figure 5b: $\delta_2(t)$ for O1 in non-epileptic subject (20 minute epoch)

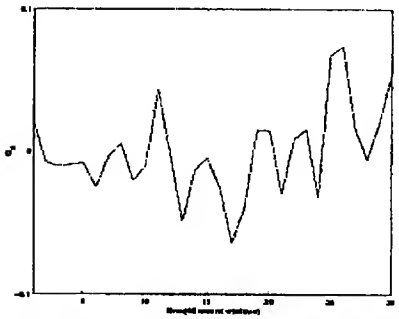

Figure 5c: $Q_2(F7, O1; t)$ for non-epileptic subject (20 minute epoch)

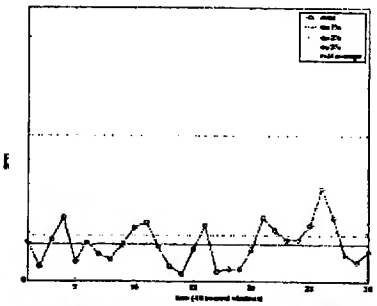

Figure 6: SPR for Q_2 interictally between electrodes remote and adjacent to site of ictal onset (See text for further explanation)

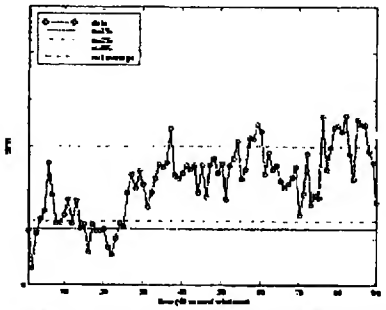

Figure 7: SPR for Q_2 preictally between electrodes remote and adjacent to site of ictal onset (See text for further explanation)

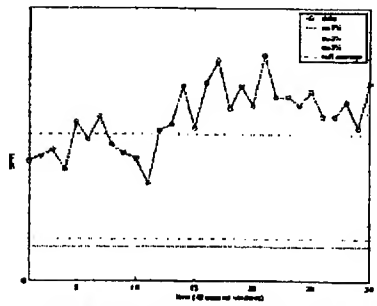

Figure 8: SPR for $Q_2(F7, O2; t)$ for non-epileptic subjects(See text for further explanation).

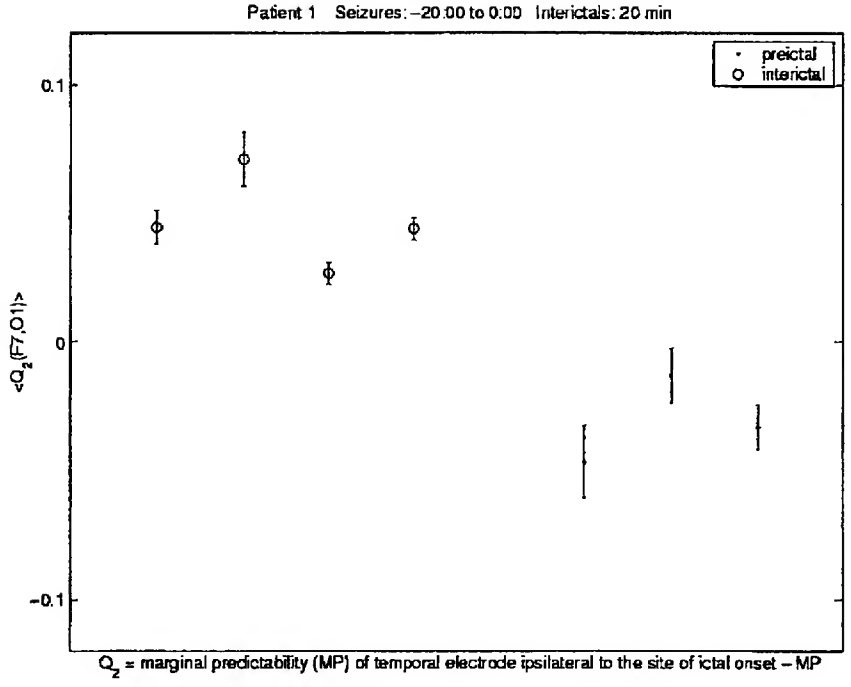

Figure 9: Q2 for 4 interictal and 3 preictal epochs for one patient

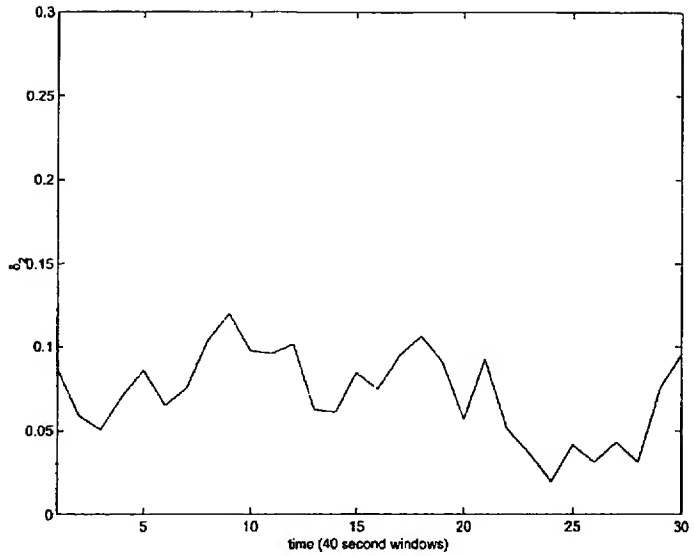

Figure 2a: interictal $\delta_2(t)$ for F8 (20 minute epoch)

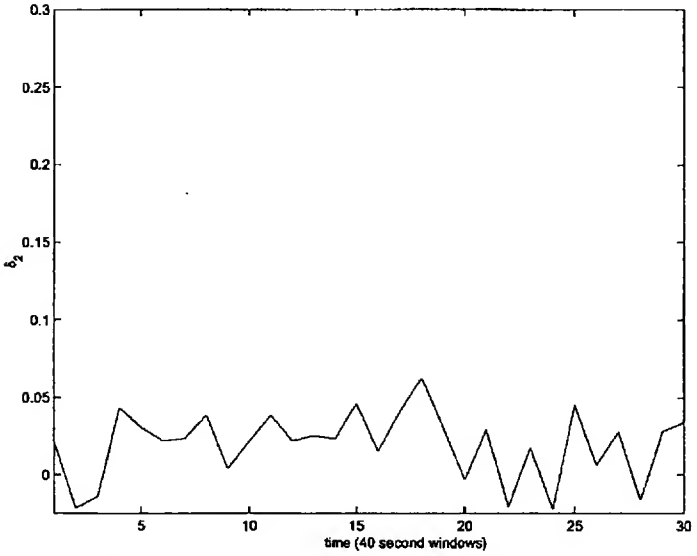

Figure 2b: interictal $\delta_2(t)$ for F8 (20 minute epoch)

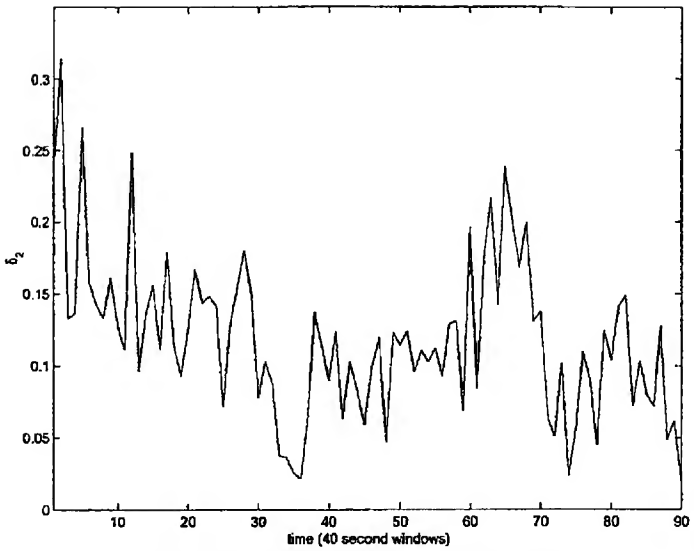

Figure 3a: preictal $\delta_2(t)$ for F8 (60 minute epoch)

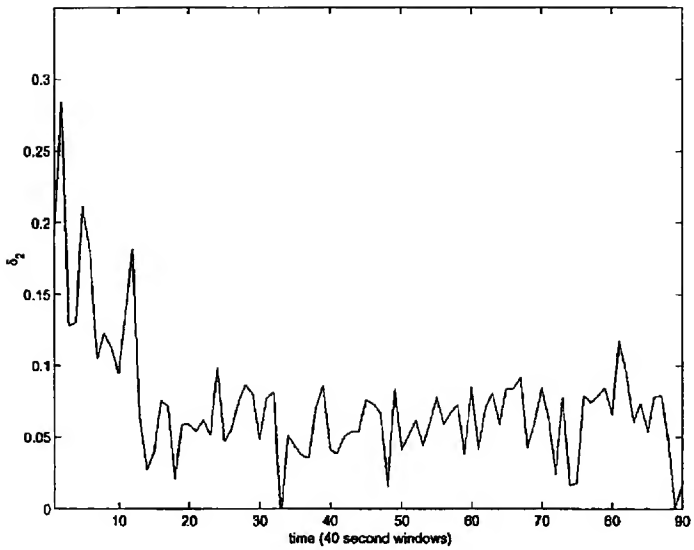

Figure 3b: preictal $\delta_2(t)$ for O2 (60 minute epoch)

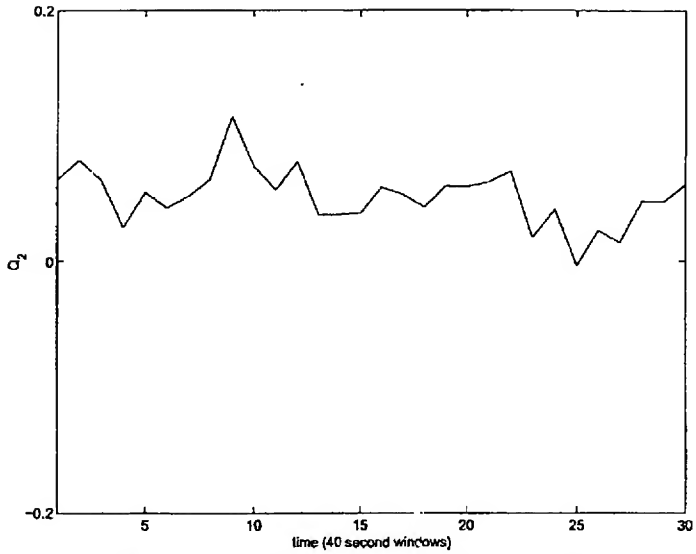

Figure 4a: interictal $Q_2(F8, O2; t)$ (20 minute epoch)

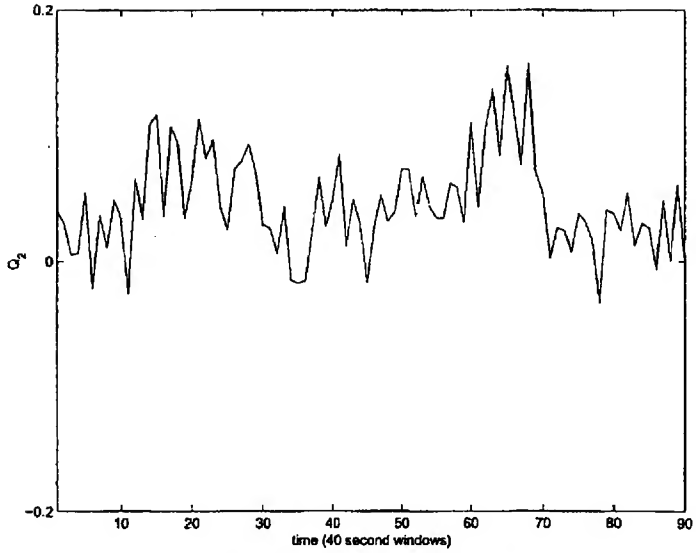

Figure 4b: preictal $Q_2(F8, O2; t)$ (60 minute epoch)

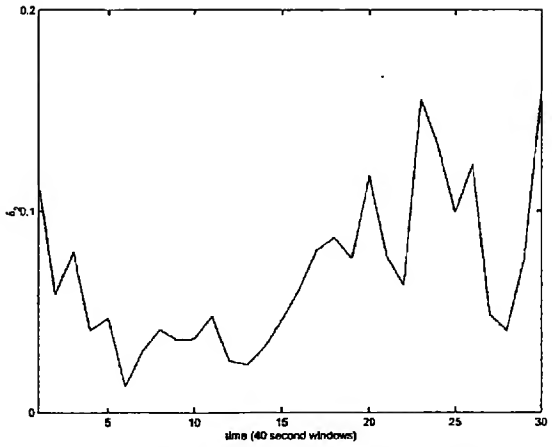

Figure 5a: $\delta_2(t)$ for F7 in a non-epileptic subject (20 minute epoch)

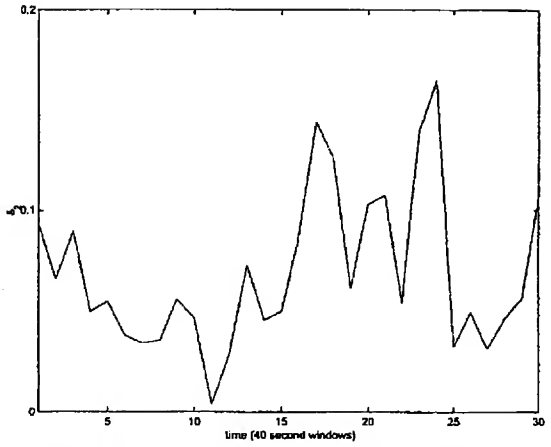

Figure 5b: $\delta_2(t)$ for O1 in a non-epileptic subject (20 minute epoch)

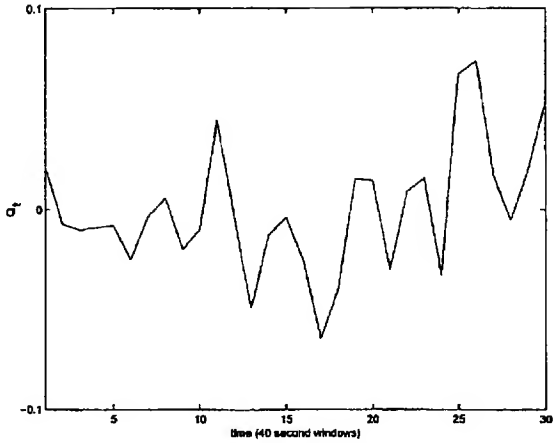

Figure 5c: $Q_2(F7, O1; t)$ for a non-epileptic subject (20 minute epoch)

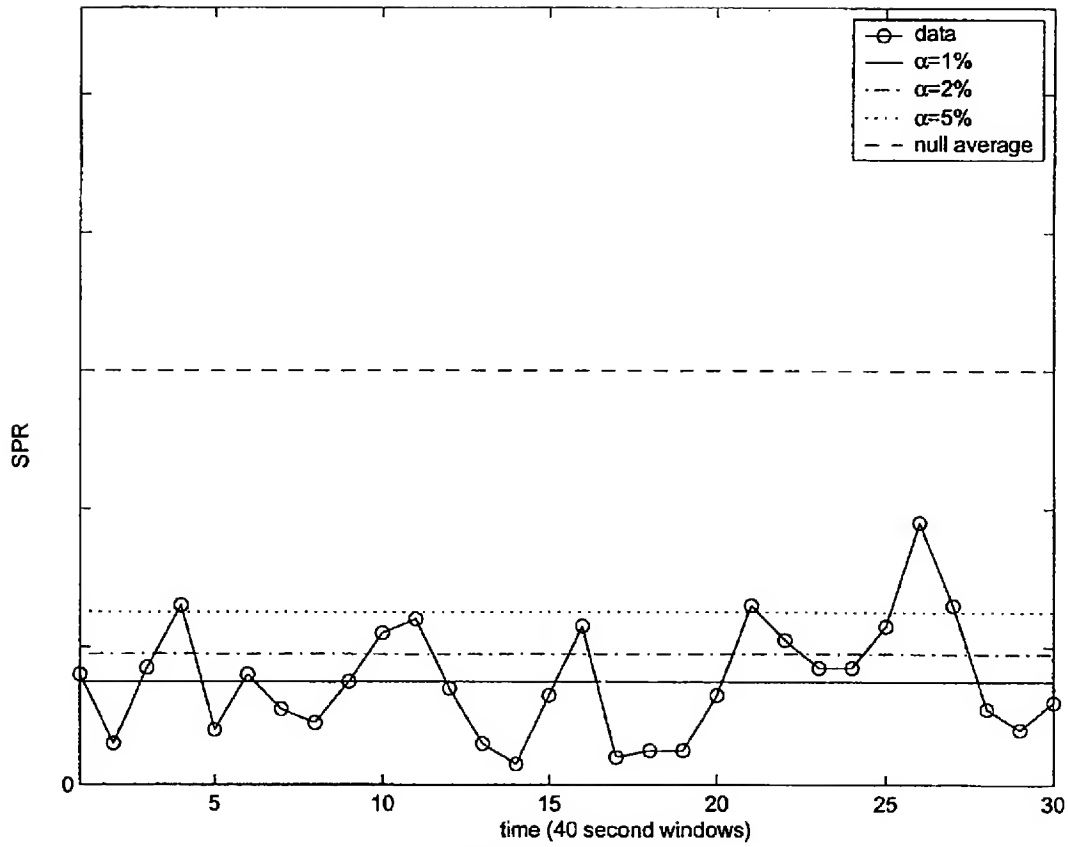

Figure 6: SPR for Q_2 interictally between electrodes remote and adjacent tosite of ictal onset (See text for further explanation)

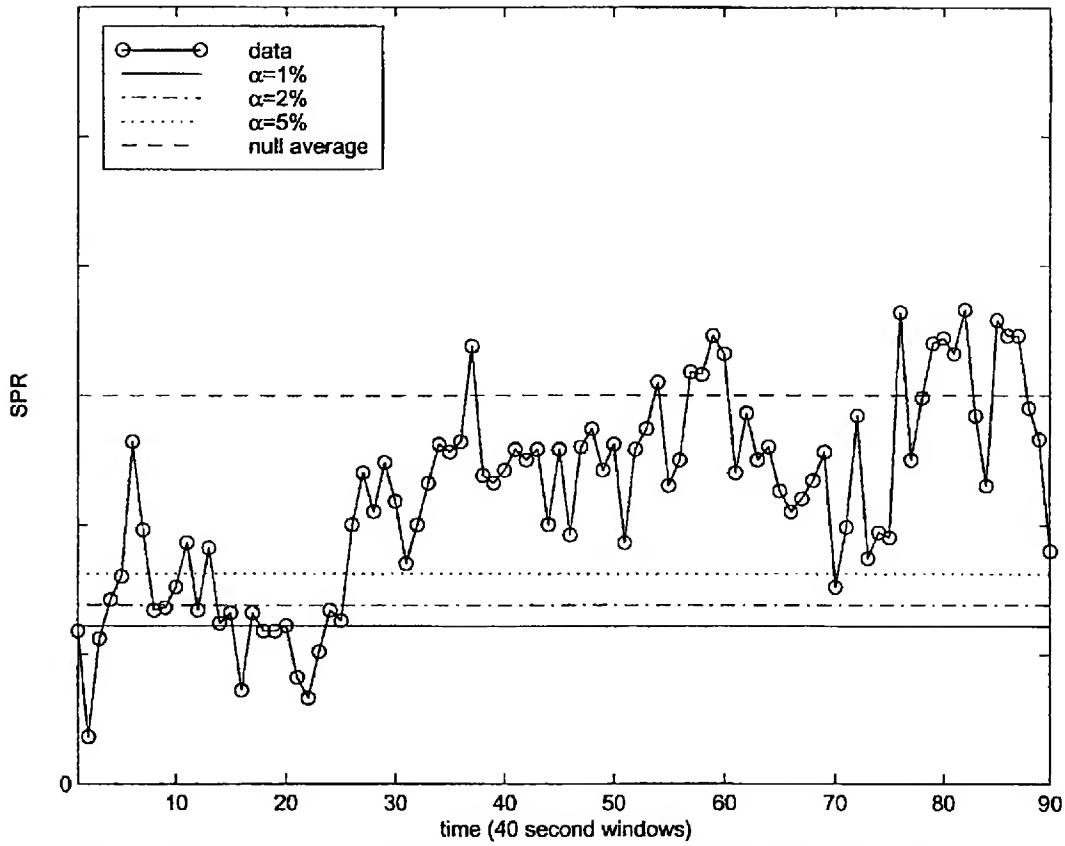

Figure 7: SPR for Q_2 preictally between electrodes remote and adjacent tosite of ictal onset (See text for further explanation)

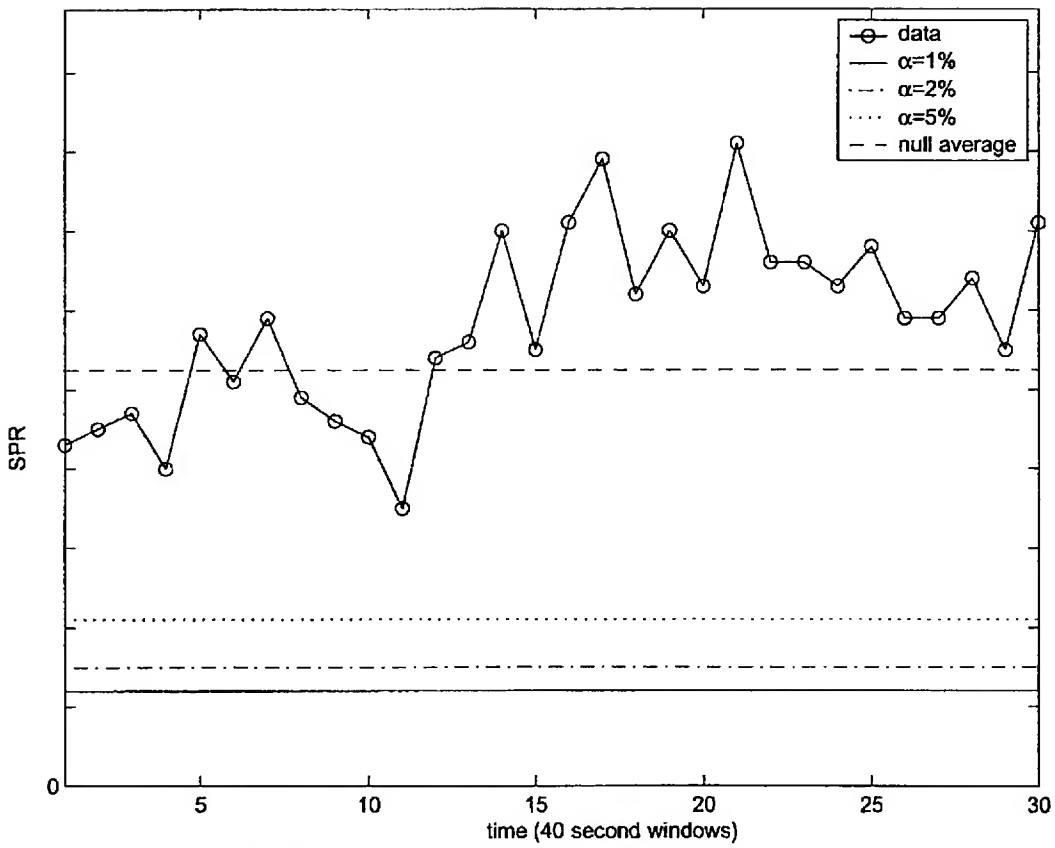

Figure 8: SPR for $Q_2(F7, O1; t)$ for non-epileptic subjects(See text for further explanation)

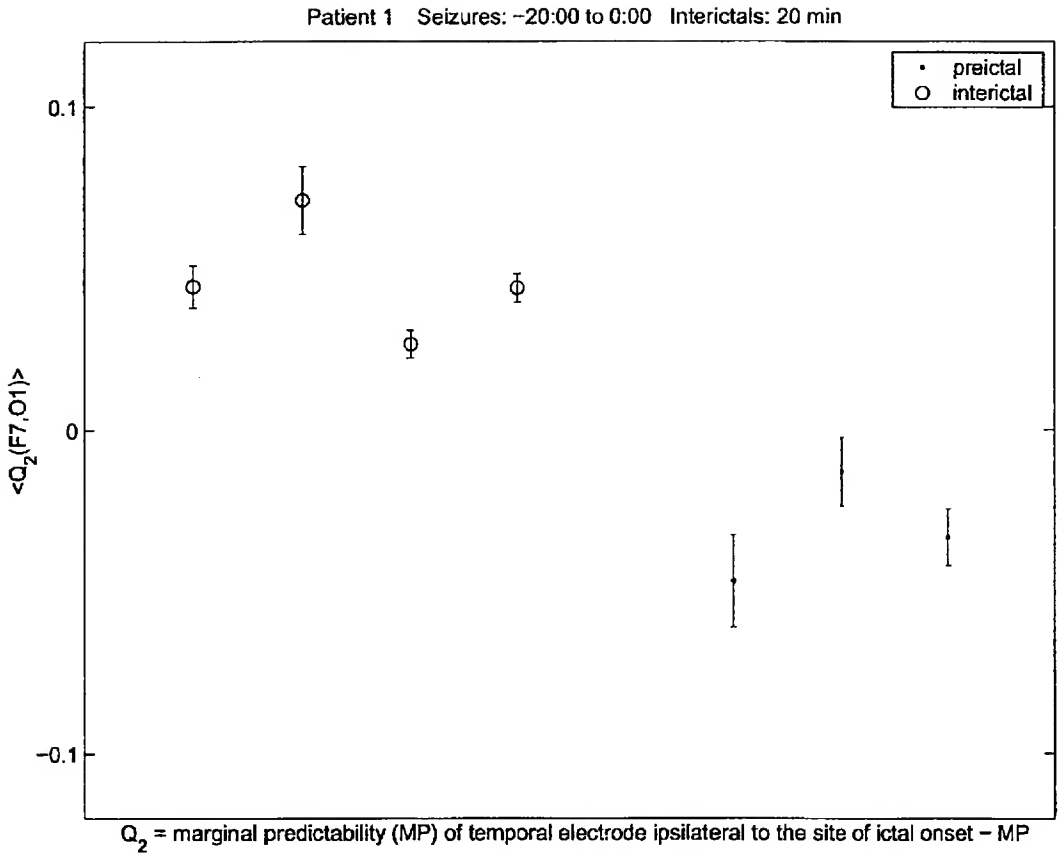

Figure 9: Q2 for 4 interictal and 3 preictal epochs for one patient